

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 074532

Trade Name : CAPTOPRIL TABLETS USP

Generic Name: Captopril Tablets USP 12.5mg, 25mg, 50mg, and 100mg

Sponsor : Wockhardt Limited

Approval Date: March 28, 1997

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APPLICATION **074532**

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074532

APPROVAL LETTERS

MARCH 28 1997

Wockhardt Limited
Attention: Mr. I.R. Berry (Agent)
Wockhardt Americas Inc.
1000 Nottingham Way
Hamilton, New Jersey 08609

Dear Sir:

This is in reference to your abbreviated new drug application dated August 11, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Captopril Tablets USP, 12.5 mg, 25 mg, 50 mg, and 100 mg.

Reference is also made to your amendments dated December 15, 1995; August 12, 1996; and January 16, February 3, and February 14, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Captopril Tablets USP, 12.5 mg, 25 mg, 50 mg, and 100 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Capoten^R Tablets 12.5 mg, 25 mg, 50 mg and 100 mg, respectively, of Bristol Meyers Squibb Company. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

3/28/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074532

FINAL PRINTED LABELING

CAPTOPRIL TABLETS, USP

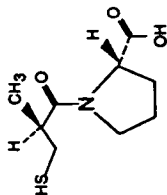
SPACE
FOR
BARCODE

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPTOPRIL should be discontinued as soon as possible. See WARNINGS: Fetal / Neonatal Morbidity and Mortality.

DESCRIPTION

Captopril is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II. Captopril is designated chemically as L-(2S)-3-mercapto-2-methylpropionyl-L-proline. Molecular formula $C_{14}H_{19}NO_5$ [MW 277.29] and has the following structural formula:



Captopril is a white to off-white crystalline powder that may have a slight sulfurous odor; it is soluble in water (approx. 160 mg/mL), methanol, and ethanol and sparingly soluble in chloroform and ethyl acetate. Each scored tablet, for oral administration, contains 12.5 mg, 25 mg, 50 mg, or 100 mg of captopril. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, corn starch, anhydrous lactose, colloidal silicon dioxide, talc and palmitic acid.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of captopril has not yet been fully elucidated. Its beneficial effects in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention. Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidylglycyl carboxyl hydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. In animal studies, captopril did not alter the pressor responses to a number of other agents, including angiotensin II and norepinephrine, indicating specificity of action.

ACE is identical to "bradykinase", and captopril may also interfere with the degradation of the vasodepressor peptide, bradykinin. Increased concentrations of bradykinin or prostaglandin E_2 may also have a role in the therapeutic effect of Captopril.

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, small increases in serum potassium may occur along with sodium and fluid loss.

The antihypertensive effects persist for a longer period of time than does demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

Pharmacokinetics

After oral administration of therapeutic doses of captopril, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent; captopril therefore should be given one hour before meals. Based on carbon-14 labeling, average minimal absorption is approximately 75 percent. In a 24-hour period, over 95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent is unchanged drug; most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide.

Approximately 25 to 30 percent of the circulating drug is bound to plasma proteins. The apparent elimination half-life for total radioactivity in blood is probably less than 3 hours. An accurate determination of half-life of unchanged captopril is not, at present, possible, but it is probably less than 2 hours. In patients with renal impairment, however, retention of captopril occurs (see DOSAGE AND ADMINISTRATION).

Pharmacodynamics

Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal blood flow following administration of captopril and glomerular filtration rate is usually unchanged. Reductions of blood pressure are usually maximal 60 to 90 minutes after oral administration of an individual dose of captopril. The duration of effect is dose related. The

CAPTOPRIL TABLETS, USP

reduction in blood pressure may be progressive, so to achieve maximal therapeutic effects, several weeks of therapy may be required. The blood pressure lowering effects of captopril and thiazide-type diuretics are additive. In contrast, captopril and beta-blockers have a less than additive effect. Blood pressure is lowered to about the same extent in both standing and supine positions. Orthostatic effects and tachycardia are infrequent but may occur in volume-depleted patients. Abrupt withdrawal of captopril has not been associated with a rapid increase in blood pressure.

In patients with heart failure, significantly decreased peripheral (systemic vascular) resistance and blood pressure (afterload), reduced pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, increased cardiac output, and increased exercise tolerance time (ETT) have been demonstrated. These hemodynamic and clinical effects occur after the first dose and appear to persist for the duration of therapy. Placebo-controlled studies of 12 weeks duration in patients who did not respond adequately to diuretics and digitalis show no tolerance to beneficial effects on ETT; open studies, with exposure up to 18 months in some cases, also indicate that ETT benefit is maintained. Clinical improvement has been observed in some patients where acute hemodynamic effects were minimal.

The Survival and Ventricular Enlargement (SAVE) study was a multicenter, randomized, double-blind, placebo-controlled trial conducted in 2,231 patients (age 21-79 years) who survived the acute phase of a myocardial infarction and did not have active ischemia. Patients had left ventricular dysfunction (LVD), defined as a resting left ventricular ejection fraction $\leq 40\%$, but at the time of randomization were not sufficiently symptomatic to require ACE inhibitor therapy for heart failure. About half of the patients had had symptoms of heart failure in the past. Patients were given a test dose of 6.25 mg oral captopril tablets and were randomized within 3-16 days post infarction to receive either captopril tablets or placebo in addition to conventional therapy. Captopril tablets was initiated at 6.25 mg or 12.5 mg tid and after two weeks titrated to a target maintenance dose of 50 mg tid. About 80% of patients were receiving the target dose at the end of the study. Patients were followed for a minimum of two years and for up to five years, with an average follow-up of 3.5 years.

Baseline blood pressure was 113/70 mm Hg and 112/70 mm Hg for the placebo and captopril tablets groups, respectively. Blood pressure increased slightly in both treatment groups during the study and was somewhat lower in the captopril tablets group (119/74 Vs. 125/77 mm Hg at 1 yr).

Therapy with captopril tablets improved long-term survival and clinical outcomes compared to placebo. The risk reduction for all cause mortality was 19% ($P=0.02$) and for cardiovascular death was 21% ($P=0.014$). Captopril treated subjects had 22% ($P=0.034$) fewer first hospitalizations for heart failure. Compared to placebo, 22% fewer patients receiving captopril developed symptoms of overt heart failure. There was no significant difference between groups in total hospitalizations for all cause (2056 placebo; 2036 captopril).

Captopril tablets were well tolerated in the presence of other therapies such as aspirin, beta blockers, nitrates, vasodilators, calcium antagonists and diuretics.

In a multicenter, double-blind, placebo-controlled trial, 409 patients, age 18-49 of either gender, with or without hypertension, with type I (juvenile type, onset before age 30) insulin-dependent diabetes mellitus, retinopathy, proteinuria ≥ 500 mg per day and serum creatinine ≤ 2.5 mg/dL, were randomized to placebo or captopril tablets (25 mg tid) and followed for up to 4.8 years (median 3 years). To achieve blood pressure control, additional antihypertensive agents (diuretics, beta blockers, centrally acting agents or vasodilators) were added as needed for patients in both groups.

The captopril tablets group had a 51% reduction in risk of doubling of serum creatinine ($P<0.01$) and a 51% reduction in risk for the combined endpoint of end-stage renal disease (dialysis, or transplantation) or death ($P<0.01$). Captopril tablets treatment resulted in a 30% reduction in urine protein excretion within the first 3 months ($P<0.05$), which was maintained throughout the trial. The captopril tablets group had somewhat better blood pressure control than the placebo group, but the effects of captopril on renal function were greater than would be expected from the group differences in blood pressure reduction alone. Captopril tablets were well tolerated in this patient population.

In two multicenter, double-blind, placebo-controlled studies, a total of 235 normotensive patients with insulin-dependent diabetes mellitus, retinopathy and microalbuminuria (20-200 $\mu\text{g}/\text{min}$) were randomized to placebo or captopril tablets (50 mg bid) and followed for up to 2 years. Captopril tablets delayed the progression to overt nephropathy (proteinuria ≥ 500 mg/day) in both studies (risk reduction 67% to 76%; $P<0.05$). Captopril tablets also reduced the albumin excretion rate. However, the long term clinical benefit of reducing the progression from microalbuminuria to proteinuria has not been established.

Studies in rats and cats indicate that captopril does not cross the blood-brain barrier to any significant extent.

INDICATIONS AND USAGE

Hypertension: Captopril tablets are indicated for the treatment of hypertension.

In using captopril, consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS).

Captopril may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations.

Captopril is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of captopril and thiazides are approximately additive.

Heart Failure: Captopril tablets are indicated in the treatment of congestive heart failure usually in combination with diuretics and digitalis. The beneficial effect of captopril in heart failure does not require the presence of digitalis, however, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment.

Left Ventricular Dysfunction After Myocardial Infarction: Captopril tablets are indicated to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction manifested as an ejection fraction $\leq 40\%$ and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure in these patients.

Diabetic Nephropathy: Captopril tablets are indicated for the treatment of diabetic nephropathy (proteinuria ≥ 500 mg/day) in patients with type I Insulin-dependent diabetes mellitus and retinopathy. Captopril tablets decrease the rate of progression of renal insufficiency and development of serious adverse clinical outcomes (death or need for renal transplantation or dialysis).

In considering use of captopril tablets, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients (see WARNINGS: Angioedema).

CONTRAINDICATIONS

Captopril tablets are contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including captopril) may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Swelling confined to the face, mucous membranes of the mouth, lips and extremities has usually resolved with discontinuation of captopril; some cases required medical therapy. (See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS.)

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

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Neutropenia/Agranulocytosis

Neutropenia ($<1000/\text{mm}^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis.

The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In foreign marketing experience in patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia but this association has not appeared in U.S. reports.

In patients with collagen vascular disease (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7 percent of patients in clinical trials.

While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. About half of the reported cases had serum creatinine ≥ 1.6 mg/dL and more than 75 percent were in patients also receiving procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

The neutropenia has usually been detected within three months after captopril was started. Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen.

In general, neutrophils returned to normal in about two weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13 percent of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.

If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately two-week intervals for about three months, then periodically.

In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution.

All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, white cell counts should be performed without delay.

Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $< 1000/\text{mm}^3$) the physician should withdraw captopril and closely follow the patient's course.

Proteinuria

Total urinary proteins greater than 1 g per day were seen in about 0.7 percent of patients receiving captopril. About 90 percent of affected patients had evidence of prior renal disease or received relatively high doses of captopril (in excess of 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

Hypotension

Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis (see PRECAUTIONS: Drug Interactions.) In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure greater than 20 percent were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, producing either no symptoms or brief mild lightheadedness although, in rare instances it has been associated with arrhythmia or conduction defects. Hypotension was the reason for discontinuation of drug in 3.6 percent of patients with heart failure.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first two weeks of treatment and whenever the dose of captopril and/or diuretic is increased. In patients with heart failure, reducing the dose of diuretic, if feasible, may minimize the fall in blood pressure. Hypotension is not per se a reason to discontinue captopril. Some decrease of systemic blood pressure is a common and desirable observation upon initiation of captopril treatment in heart failure. The magnitude of the decrease is greatest early in the course of treatment; this effect stabilizes within a week or two, and generally returns to pretreatment levels, without a decrease in therapeutic efficacy, within two months.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure. These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

General

Impaired Renal Function

Hypertension - Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalize blood pressure and maintain adequate renal perfusion.

Heart Failure - About 20 percent of patients develop stable elevations of BUN and serum creatinine greater than 20 percent above normal or baseline upon long-term treatment with captopril. Less than 5 percent of patients, generally those with severe preexisting renal disease, required discontinuation of treatment due to progressively increasing creatinine; subsequent improvement probably depends upon the severity of the underlying renal disease.

See CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS: Altered Laboratory Findings.

Hyperkalemia: Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. (See PRECAUTIONS: Information for Patients and Drug Interactions; ADVERSE REACTIONS: Altered Laboratory Findings.)

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Vascular Stenosis: There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction as others.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hemodialysis

Recent clinical observations have shown an association of hypersensitivity-like (anaphylactoid) reactions during hemodialysis with high-flux dialysis membranes (e.g., AN69) in patients receiving ACE inhibitors. In these patients, consideration should be given to using a different type of dialysis membrane or a different class medication. (See WARNINGS: Anaphylactoid Reactions During Membrane Exposure.)

Information for Patients

Patients should be advised to immediately report to their physician any signs or symptoms suggesting angioedema (e.g., swelling of face, eyes, lips, tongue, larynx and extremities; difficulty in swallowing or breathing; hoarseness) and to discontinue therapy. (See WARNINGS: Angioedema.)

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever), which may be a sign of neutropenia, or of progressive edema which might be related to proteinuria and nephrotic syndrome.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Patients should be advised not to use potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes without consulting their physician. (See PRECAUTIONS: General and Drug Interaction; ADVERSE REACTIONS.)

Patients should be warned against interruption or discontinuation of medication unless instructed by the physician.

Heart failure patients on captopril therapy should be cautioned against rapid increase in physical activity.

Patients should be informed that captopril should be taken one hour before meals (see DOSAGE AND ADMINISTRATION).

Pregnancy/Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

Hypotension - Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril.

The possibility of hypotensive effects with captopril can be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with captopril or initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least one hour after the initial dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

Agents Having Vasodilator Activity: Data on the effect of concomitant use of other vasodilators in patients receiving captopril for heart failure are not available; therefore, nitroglycerin or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting captopril. If resumed during captopril tablet therapy, such agents should be administered cautiously, and perhaps at lower dosage.

Agents Causing Renin Release: Captopril's effect will be augmented by antihypertensive agents that cause renin release. For example, diuretics (e.g., thiazides) may activate the renin-angiotensin-aldosterone system.

Agents Affecting Sympathetic Activity: The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive.

Agents Increasing Serum Potassium: Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics such as spironolactone, triamterene, or amiloride, or potassium supplements should be given only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Salt substitutes containing potassium should also be used with caution.

Inhibitors Of Endogenous Prostaglandin Synthesis: It has been reported that indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other nonsteroidal anti-inflammatory agents (e.g., aspirin) may also have this effect.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction

Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. The high dose in these studies is 150 times the maximum recommended human dose of 450 mg, assuming a 50 kg subject. On a body-surface-area basis, the high doses for mice and rats are 13 and 26 times the maximum recommended human dose, respectively.

Studies in rats have revealed no impairment of fertility.

Animal Toxicology

Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug related toxicity included effects on hematopoiesis: renal toxicity, erosion/ulceration of the stomach and variation of retinal blood vessels.

Reductions in hemoglobin and/or hematocrit values were seen in mice, rats and monkeys at doses 50 to 150 times the maximum recommended human dose (MRHD) of 450 mg, assuming a 50 kg subject. On a body-surface-area basis, these doses are 5 to 25 times maximum recommended human dose (MRHD). Anemia, leukopenia,

thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD on a body-weight basis (4 to 15 times MRHD on a surface-area basis). The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8 to 30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1 year study. However, in the 47-week study at a dose 30 times MRHD, bone marrow suppression was found to be reversible upon continued drug administration.

Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys in mice and rats at doses 7 to 200 times MRHD on a body-weight basis (0.6 to 35 times MRHD on a surface-area basis); in monkeys at 20 to 60 times MRHD on a body-weight basis (7 to 20 times MRHD on a surface-area basis); and in dogs at 30 times MRHD on a body-weight basis (15 times MRHD on a surface-area basis).

Gastric erosions/ulcerations were increased in incidence in male rats at 20 to 200 times MRHD on a body-weight basis (3.5 and 35 times MRHD on a surface-area basis); in dogs at 30 times MRHD on a body-weight basis (15 times on MRHD on a surface-area basis); and in monkeys at 65 times MRHD on a body-weight basis (20 times MRHD on a surface-area basis). Rabbits developed gastric and intestinal ulcers when given oral doses approximately 30 times MRHD on a body-weight basis (10 times MRHD on a surface-area basis) for only 5 to 7 days.

In the two-year rat study, irreversible and progressive variations in the caliber of retinal vessels (focal secutations and constrictions) occurred at all dose levels (7 to 200 times MRHD) on a body weight basis; 1 to 35 times MRHD on a surface-area basis in a dose-related fashion. The effect was first observed in the 88th week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

Pregnancy Categories C (first trimester) and D (second and third trimesters)

See **WARNINGS : Fetal / Neonatal Morbidity and Mortality.**

Nursing Mothers

Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of captopril to the mother. (See **PRECAUTIONS : Pediatric Use.**)

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

Captopril tablets should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS

Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About one of 100 patients developed proteinuria (see **WARNINGS**).

Each of the following has been reported in approximately 1 to 2 of 1000 patients and are of uncertain relationship to drug use: renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency.

Hematologic: Neutropenia/leukocytosis has occurred (see **WARNINGS**). Cases of anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, often with pruritus, and sometimes with fever, arthralgia, and eosinophilia, occurred in about 4 to 7 (depending on renal status and dose) of 100 patients, usually during the first four weeks of therapy. It is usually maculopapular, and rarely urticarial. The rash is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, occurs in about 2 of 100 patients. Between 7 and 10 percent of patients with skin rash have shown an eosinophilia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported.

Flushing or pallor has been reported in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see **WARNINGS** and **PRECAUTIONS (Drug Interactions)** for discussion of hypotension with captopril therapy.

Tachycardia, chest pain, and palpitations have each been observed in approximately 1 of 100 patients.

Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception. Taste impairment is reversible and usually self-limited (2 to 3 months) even with continued drug administration. Weight loss may be associated with the loss of taste.

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See **WARNINGS : Angioedema** and **PRECAUTIONS: Information for Patients.**)

Cough: Cough has been reported in 0.5 to 2% of patients treated with captopril in clinical trials (see **PRECAUTIONS : General, Cough**)

The following have been reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

Body as a whole: Anaphylactoid reactions (see **WARNINGS : Anaphylactoid and Possibly Related Reactions** and **PRECAUTIONS : Hemodialysis**).

General: Asthenia, gynecostasia.

Cardiovascular: Cardiac arrest, cerebrovascular accident / insufficiency, rhythm disturbances, orthostatic hypotension, syncope.

Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.

Gastrointestinal: Pancreatitis, glossitis, dyspepsia.

Hematologic: Anemia, including aplastic and hemolytic.

Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.

Metabolic: Symptomatic hyponatremia.

Musculoskeletal: Myalgia, myasthenia.

Nervous/Psychiatric: Apathy, confusion, depression, nervousness, somnolence.

Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.

Special Senses: Blurred vision.

Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality

See **WARNINGS : Fetal/Neonatal Morbidity and Mortality.**

Altered Laboratory Findings

Serum Electrolytes: Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (see **PRECAUTIONS**).

Hyponatremia: Particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

6

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE

Correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

DOSAGE AND ADMINISTRATION

Captopril tablets should be taken one hour before meals. Dosage must be individualized. Hypertension - Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other clinical circumstances. If possible, discontinue the patient's previous antihypertensive drug regimen for one week before starting captopril. The initial dose of captopril is 25 mg bid or tid. If satisfactory reduction of blood pressure has not been achieved after one or two weeks, the dose may be increased to 50 mg bid or tid. Concomitant sodium restriction may be beneficial when captopril is used alone.

The dose of captopril in hypertension usually does not exceed 50 mg tid. Therefore, if the blood pressure has not been satisfactorily controlled after one to two weeks at this dose, (and the patient is not already receiving a diuretic), a modest dose of thiazide-type diuretic (e.g., hydrochlorothiazide, 25 mg daily), should be added. The diuretic dose may be increased at one- to two-week intervals until its highest usual antihypertensive dose is reached.

If captopril is being started in a patient already receiving a diuretic, captopril therapy should be initiated under close medical supervision (see WARNINGS and PRECAUTIONS [Drug Interactions]) regarding hypotension, with dosage and titration of captopril as noted above.

If further blood pressure reduction is required, the dose of captopril may be increased to 100 mg bid or tid and then, if necessary, to 150 mg bid or tid (while continuing the diuretic). The usual dose range is 25 to 150 mg bid or tid. A maximum daily dose of 450 mg captopril should not be exceeded.

For patients with severe hypertension (e.g., accelerated or malignant hypertension), when temporary discontinuation of current antihypertensive therapy is not practical or desirable, or when prompt titration to more normotensive blood pressure levels is indicated, diuretic should be continued but other current antihypertensive medication stopped and captopril dosage promptly initiated at 25 mg bid or tid, under close medical supervision.

When necessitated by the patient's clinical condition, the daily dose of captopril may be increased every 24 hours or less under continuous medical supervision until a satisfactory blood pressure response is obtained or the maximum dose of captopril is reached. In this regimen, addition of a more potent diuretic, e.g., furosemide, may also be indicated.

Beta-blockers may also be used in conjunction with captopril therapy (see PRECAUTIONS [Drug Interactions]), but the effects of the two drugs are less than additive. Heart Failure - Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. In patients with either normal or low blood pressure, who have been vigorously treated with diuretics and who may be hyponatremic and/or hypovolemic, a starting dose of 6.25 or 12.5 mg tid may minimize the magnitude or duration of the hypotensive effect (see WARNINGS, [Hypotension]); for these patients, titration to the usual daily dosage can then occur within the next several days.

For most patients the usual initial daily dosage is 25 mg tid. After a dose of 50 mg tid is reached, further increases in dosage should be delayed, where possible, for at least two weeks to determine if a satisfactory response occurs. Most patients studied have had a satisfactory clinical improvement at 50 or 100 mg tid. A maximum daily dose of 450 mg of captopril should not be exceeded.

Captopril should generally be used in conjunction with a diuretic and digitalis. Captopril therapy must be initiated under very close medical supervision. Left Ventricular Dysfunction After Myocardial Infarction - The recommended dose for long-term use in patients following a myocardial infarction is a target therapy may be initiated as early as three days following a myocardial infarction. After a single dose of 6.25 mg, captopril tablets therapy should be initiated at 12.5 mg tid. Captopril tablets should then be increased to 25 mg tid during the next several days and to a target dose of 50 mg tid over the next several weeks as tolerated (see CLINICAL PHARMACOLOGY).

Captopril tablets may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, aspirin, beta blockers.

Diabetic Nephropathy: The recommended dose of captopril tablets for long term use to treat diabetic nephropathy is 25 mg tid. Other antihypertensives such as diuretics, beta blockers, centrally acting agents or vasodilators may be used in conjunction with captopril tablets if additional therapy is required to further lower blood pressure.

Dosage Adjustment in Renal Impairment - Because captopril is excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher steady-state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses.

Accordingly, for patients with significant renal impairment, initial daily dosage of captopril should be reduced, and smaller increments utilized for titration, which should be quite slow (one- to two-week intervals). After the desired therapeutic effect has been achieved, the dose should be slowly back titrated to determine the minimal effective dose. When concomitant diuretic therapy is required, a loop diuretic (e.g., furosemide), rather than a thiazide diuretic, is preferred in patients with severe renal impairment. (See WARNINGS: Anaphylactoid reactions during membrane exposure and PRECAUTIONS: Hemodialysis.)

HOW SUPPLIED

12.5 mg Captopril tablets in bottles of 100 (NDC 55648 - 902 - 01) and 1000 (NDC 55648 - 902 - 02), 25 mg Captopril tablets in bottles of 100 (NDC 55648 - 903 - 01) and 1000 (NDC 55648 - 903 - 02), 50 mg Captopril tablets in bottles of 100 (NDC 55648 - 904 - 01) and 1000 (NDC 55648 - 904 - 02), and 100 mg Captopril tablets in bottles of 100 (NDC 55648-905-01). Bottles contain a desiccant - Charcoal canister.

The 12.5 mg tablet is white, flat bevelled-edge round with a bisect bar on one side and W on the other side; the 25 mg Captopril tablet is a white, flat bevelled-edge round with a quadrisect bar on one side and W on the other side; the 50 mg Captopril tablet is a white, flat bevelled-edge round with a bisect bar on one side and W on the other side; the 100 mg Captopril tablet is a white, flat bevelled-edge round with a bisect bar on one side and W on the other side.

All captopril tablets are white and may exhibit a slight sulfurous odor.

CAUTION: Federal Law prohibits dispensing without prescription.

Dispense in a tight container as defined in the USP.

Storage

Do not store above 86° F. Keep bottles tightly closed (protect from moisture).

Manufactured in India
WOCKHARDT LTD.
Mumbai- 400 018, INDIA.

Distributed by:
AccuMed Pharmaceuticals Inc.
Hamilton, NJ 08609

Revised: 02 / 97.

Each tablet contains
12.5 mg captopril, USP

Manufactured in India
WOCKHARDT LTD.
Mumbai - 400 018
INDIA.

Distributed by
AccuMed
Pharmaceuticals Inc.
Hamilton, NJ 08609

100 tablets NDC 55648-902-01

12.5 mg

Captopril
Tablets, USP

Caution : Federal law prohibits
dispensing without prescription.
Dispense in a tight container, as
defined in the USP.

Keep tightly closed (protect from moisture)
Do not store above 86°F
Usual Dosage : see package insert

28 1997

Each tablet contains
12.5 mg captopril, USP

Manufactured in India
WOCKHARDT LTD.
Mumbai - 400 018
INDIA.

Distributed by
AccuMed
Pharmaceuticals Inc.
Hamilton, NJ 08609

1000 tablets NDC 55648-902-02

12.5 mg

Captopril
Tablets, USP

Caution : Federal law prohibits
dispensing without prescription.
Dispense in a tight container, as
defined in the USP.

Keep tightly closed (protect from moisture)
Do not store above 86°F
Usual Dosage : see package insert

28 1997

Each tablet contains
100 mg captopril, USP

Manufactured in India
WOCKHARDT LTD.
Mumbai - 400 018
INDIA.

Distributed by
AccuMed
Pharmaceuticals Inc.
Hamilton, NJ 08609

100 tablets NDC 55648-905-01

100 mg

Captopril
Tablets, USP

Caution : Federal law prohibits
dispensing without prescription.
Dispense in a tight container, as
defined in the USP.

Keep tightly closed (protect from moisture)
Do not store above 86°F
Usual Dosage : see package insert

28 1997

Each tablet contains
25 mg captopril, USP

Manufactured in India
WOCKHARDT LTD.
Mumbai - 400 018
INDIA.

Distributed by
AccuMed
Pharmaceuticals Inc.
Hamilton, NJ 08609

1000 tablets

NDC 55648-903-02

25 mg

Captopril
Tablets, USP

Caution : Federal law prohibits
dispensing without prescription.
Dispense in a tight container, as
defined in the USP.

Keep tightly closed (protect from moisture)
Do not store above 86°F
Usual Dosage : see package insert

Each tablet contains
25 mg captopril, USP

Manufactured in India
WOCKHARDT LTD.
Mumbai - 400 018
INDIA

Distributed by
AccuMed
Pharmaceuticals Inc.
Hamilton, NJ 08609

100 tablets
25 mg

NDC 55648-903-01

Captopril
Tablets, USP

Caution : Federal law prohibits
dispensing without prescription.
Dispense in a tight container, as
defined in the USP.

Keep tightly closed (protect from moisture)
Do not store above 86°F
Usual Dosage : see package insert

2 8 1997

Each tablet contains
50 mg captopril, USP

Manufactured in India
WOCKHARDT LTD.
Mumbai - 400 018
INDIA.

Distributed by
AccuMed
Pharmaceuticals Inc.
Hamilton, NJ 08609

1000 tablets

NDC 55648-904-02

50 mg

Captopril
Tablets, USP

Caution : Federal law prohibits
dispensing without prescription.
Dispense in a tight container, as
defined in the USP.

Keep tightly closed (protect from moisture)
Do not store above 86°F
Usual Dosage : see package insert

2 8 1997

Each tablet contains
50 mg captopril, USP

Manufactured in India
WOCKHARDT LTD.
Mumbai - 400 018
INDIA.

Distributed by
AccuMed
Pharmaceuticals Inc.
Hamilton, NJ 08609

100 tablets

NDC 55648-904-01

50 mg

Captopril
Tablets, USP

Caution : Federal law prohibits
dispensing without prescription.
Dispense in a tight container, as
defined in the USP.

Keep tightly closed (protect from moisture)
Do not store above 86°F
Usual Dosage : see package insert

MAR 2 8 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074532

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 4 2. ANDA # 74-532
3. NAME AND ADDRESS OF APPLICANT
Wockhardt. Ltd., Attention: Mr. A.S. Gosavi
Poonam chamgers, Dr Annie Besant Road, Worli, Bombay 400 018
US Agent: Wockhardt Americas Inc. Attention: Mr. I.R. Berry
1000 Nottingham Way, Hamilton, New Jersey 08609
4. BASIS OF SUBMISSION Capoten® Bristol-Myers Squibb
Patent 4105776/08-08-95, exclusivity I-95/09-23-96 and I-
101/01-28-97 (ref. Orange Book 16th edition, cum. supp. 10)
7. NONPROPRIETARY NAME Captopril Tablets, USP
9. AMENDMENTS AND OTHER DATES:
02-14-97 T-Con Fax Amendment - this review
02-03-97 Facsimile Minor Amendment- this review
01-16-97 New Correspondence for labeling
01-14-97 Minor Deficiency Letter Faxed to firm
08-12-96 Major Amendment
03-22-96 Chemistry Major Deficiency Letter #2
02-14-96 Labeling Review #2-deficient
02-06-96 Bio Approve
12-15-95 New Correspondence-Bio
07-21-95 Labeling amendment
07-19-95 New Correspondence for Bio
07-07-95 Major Amendment
06-10-95 New Correspondence-patent certification
05-05-95 CMC 1st review-J. Fan
03-21-95 Labeling Review-deficient
01-06-95 Filing Letter
05-24-95 Bio Review
11-28-94 Original amendment-in response to RF letter
10-06-94 Refusal to File Letter
08-11-94 original submission
10. PHARMACOLOGICAL CATEGORY Anti-hypertensive 11. Rx
13. DOSAGE FORM and 14. POTENCY
12.5 mg round, flat, bevelled-edge scored tablet debossed "W 902" . 25.0 mg round, flat, bevelled-edge tablet cross
scored debossed "W 903", 50.0 mg round, flat, bevelled-edge scored tablet debossed "W 904" and 100.0 mg
round, flat, bevelled-edge scored tablet debossed "W 904"
18. CONCLUSIONS AND RECOMMENDATIONS T-CON ⇒ **APPROVE**
19. REVIEWER Melissa Maust DATE COMPLETED February 12, 1997
cc: ANDA 74-532 REVISED: March 12, 1997
 DUP Jacket
 Division File
 Field Copy
- Endorsements:
HFD-623/M.Maust. 2-12-97 3/12/97
HFD-623/V.Sayed, Ph.D./
Y:\NEW\FIRMSNZ\WOCKHARD\LTRS&REV\74532R4.AP
F/T by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074532

BIOEQUIVALENCE REVIEW(S)

MAY 24 1995

Captopril Tablets
12.5 mg, 25 mg, 50 mg and 100 mg
ANDA #74-532
Reviewer: Sikta Pradhan
WP #74532SDW.N94

Wockhardt Ltd.
Bombay, India
Submission Date:
November 28, 1994

Review of a Bioequivalence Study and Waiver Requests

I. INTRODUCTION:

Captopril, a specific inhibitor of angiotensin I converting enzyme (ACE) is indicated for the treatment of hypertension and congestive heart failure. After an oral administration, the drug is readily absorbed (60-75%) from the gastrointestinal (GI) tract in fasting healthy adults or hypertensive patients. The presence of food in the GI tract reduces absorption by about 30 to 40 percent. Captopril is approximately 25-30% bound to plasma proteins. Areas under the concentration-time curve (AUC) and maximum blood concentrations (Cmax) after single oral doses of captopril appear to be dose-related over a range of 10 to 100 mg. About half the absorbed dose of captopril is rapidly metabolized, mainly to captopril-cysteine disulfide and to the disulfide dimer of captopril. Captopril and its metabolites are excreted in the urine. The elimination half-life of captopril has been reported to be about two hours.

The initial dose of captopril is 25 mg *bid* or *tid*. The dose is increased to 50 mg *bid* or *tid* after one or two weeks if the lower dose is ineffective. It is labeled to be dosed one hour before meal. Captopril is currently available as Capoten^R (Squibb) in 12.5, 25, 50 mg and 100 mg tablets for oral administration.

The present submission provides the reports of a bioequivalence study comparing the test product, 100 mg tablets of Wockhardt Ltd. with the reference product, Capoten^R 100 mg tablets, manufactured by E.R. Squibb & Sons, Inc.

In-Vivo Study:

The clinical study was conducted at the
under the supervision of

Study Design:

A randomized 2-way crossover, single dose bioequivalence study on the test product, Captopril, 100 mg tablet (Wockhardt) and reference product, Capoten^R 100 mg tablet was conducted according to protocol # 940306

Subjects: Twenty-six healthy male volunteers between 18-45 years of age and within $\pm 15\%$ of their ideal body weight according to Metropolitan Life Insurance Company Bulletin, 1983, were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Tests (hematology, blood chemistry, urinalysis, etc.) The subjects were restricted from all medications for two weeks prior to the first drug administration until after the study was completed. The volunteers were not allowed to drink alcoholic beverages for 24 hours before dosing and throughout the period of sample collection. The subjects were randomly divided into two dosing groups of equal numbers.

Treatments:

- A. 1 x 100 mg Captopril tablet (Wockhardt), Lot # 94001-D,
Lot size: Potency: Not provided
- B. 1 x 100 mg Capoten^R tablet (Squibb), Lot # H3J73A
Potency: Not provided, Expiry date: October, 1998.

Dose Administration: A single dose of 100 mg Captopril was administered with 240 mL of water.

Drug Washout Period: One week.

Meal and Food Restrictions: All volunteers fasted for 10 hours prior to and 4 hours after drug administration. Fluids were restricted within one hour of dosing. Standard meal was served. No caffeine-containing food or beverage was served during the study.

Blood Sample Collection:

Ten (2x5) milliliters of venous blood were collected in two chilled

vacutainers containing EDTA before dosing at 0 and five (5 mL) at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 7, 8 and 10 hours after dosing. The whole blood samples were kept frozen at -80°C till analysis.

Assay Methodology:

Results:

Twenty-six (26) volunteers were selected for the study. All twenty-six (26) volunteers completed the study. Samples from the first 24 subjects were analyzed. Sitting blood pressure and heart rate of each subject were measured at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hr. No abnormal measurements were observed. The non-serious adverse events experienced by some subjects have been reported in Table 1 (attached). Mean (whole blood) captopril levels and the pharmacokinetic parameters derived from them are presented in Table 2 and Table 3, respectively.

Table 2
Mean Blood Captopril Levels (ng/mL)
(1X100 mg Dose; 24 Subjects)

Time (hour)	TEST (A) (Wockhardt) Lot #94001-D	Reference (B) (Squibb) Capoten ^R Lot #H3J73A	Signif. Diff. at p=0.05
Pre-dose	0	0	---
0.25	92,33 (89) *	137.37 (85)	<u>Not Provided</u>
0.50	532.93 (46)	623.99 (44)	"
0.75	790.67 (28)	826.99 (29)	"
1.0	727.46 (16)	689.50 (24)	"
1.25	574.87 (18)	545.53 (23)	"
1.50	418.27 (23)	397.99 (24)	"
1.75	310.33 (26)	314.81 (32)	"
2.00	246.65 (38)	240.37 (36)	"
2.33	171.78 (39)	164.66 (33)	"
2.67	114.75 (39)	110.99 (30)	"
3.0	87.34 (36)	85.54 (30)	"
3.33	63.22 (35)	59.30 (27)	"
3.67	49.13 (35)	45.91 (28)	"
4.00	37.81 (26)	36.68 (27)	"
4.5	21,26 (66)	23.77 (44)	"
5.00	15.37 (80)	13.13 (98)	"
6.00	0.91 (490)	1.91 (339)	"
7.00	0	0	"
8.00	0	0	"
10.00	0	0	"

* Coefficient of Variation

Table 3
Mean Pharmacokinetic Parameters for Blood Captopril Levels
(1X100 mg Dose; 24 Subjects)

<u>Parameters</u>	<u>Test (A)</u>	<u>Ref. (B)</u>	<u>A/B%</u>
AUC _{0-T} (ng.hr/mL)	1124.4 (15)*	1139.5 (16)	98.7
AUC _{0-inf} (ng.hr/mL)	1159.0 (14)	1172.8 (16)	98.8
C _{MAX} (ng/mL)	840.49 (18)	870.18 (28)	96.6
T _{max} (hour)	0.896 (32)	0.792 (29)	
t _{1/2} (hour)	0.972 (23)	0.975 (21)	
KE (1/hour)	0.7398 (17)	0.7363 (18)	

()* Coefficient of Variation

Pharmacokinetic Parameters derived from LS Means:

<u>Parameters</u>	<u>Test (A)</u>	<u>Ref. (B)</u>	<u>A/B</u>	<u>90% C.I.</u>
LnAUC _{0-T}	7.01 [0.157]**	7.03 [0.167]	0.99	95; 103
LnAUC _{0-inf}	7.04 [0.153]	7.05 [0.164]	0.99	95; 103
LnC _{MAX}	6.717 [0.189]	6.741 [0.241]	0.98	89; 107

[]** Standard Deviation
Number of Subjects 24

Both test and reference drugs produced peak concentration between 0.5 to 1 hour after their administration (see Table 2 and Figures 1&2, attached). The differences between the test and reference products in LnAUC_{0-T}, LnAUC_{0-inf} and LnC_{MAX} were 2% or less. All these differences were statistically insignificant. The ratio analysis of the test and reference AUC_{0-T}, AUC_{0-inf} and C_{MAX} are presented in Tables 4-6. The 90% confidence intervals for LnAUC_{0-T}, LnAUC_{0-inf} and LnC_{MAX} of the test product remained within the 80% to 125% limit of the corresponding reference mean values.

In-Vitro Dissolution:

The firm has conducted an acceptable dissolution testing on Captopril tablets. Both USP and FDA dissolution methods are identical. The dissolution testing data are presented in Table 7 below:

Table 7. In Vitro Dissolution Testing

Drug: Captopril
Dose Strengths: 12.5 mg, 25 mg, 50 mg and 100 mg Tablets
ANDA No.: 74-532
Firm: Wockhardt Limited
Submission Date: November 28, 1994

I. Conditions for Dissolution Testing: "NOT PROVIDED"

USP XXII Basket **RPM:** _____
No. Units Tested: 12
Medium: 0.1N HCl **Volume:** mL
Specifications: NLT (Q) of the labeled amount is dissolved
 in 20 minutes.
Reference Drug: Squibb's CapotenR Tabs (12.5, 25, 50 and 100 mg)
Assay Methodology: USP XXII

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 94001D Strength 100 mg Tablets			Reference Product Lot # C2K83B Strength 100 mg Tablets		
	Mean %	Range	%CV	Mean %	Range	%CV
10	94.46		1.73	89.01		3.24
20	97.08		1.73	94.05		1.99
30	99.80		1.53	98.19		1.02
Sampling Times (Minutes)	Test Product Lot # 94001C Strength 50 mg Tablets			Reference Product Lot # B3J73A Strength 50 mg Tablets		
10	97.51		2.55	89.01		3.24
20	96.14		2.90	94.05		1.99
30	100.68		1.56	98.19		1.02
Sampling Times (Minutes)	Test Product Lot # 94001B Strength 25 mg Tablets			Reference Product Lot # 1A61681 Strength 25 mg Tablets		
10	98.16		3.37	61.18		18.9
20	99.70		2.83	85.72		10.2
30	101.14		2.37	96.71		4.5
Sampling Times (Minutes)	Test Product; Lot #94001A Strength 12.5 mg Tablets			Reference Prod.; Lot #A3 J3 Strength 12.5 mg Tablets		
10	93.01		12.1	86.42		16.8
20	100.01		5.12	97.48		6.29
30	99.83		4.54	98.75		4.58

Formulations:

The compositions of Captopril Tablets, 100 mg, 50 mg, 25 mg and 12.5 mg are presented below:

<u>Ingredient</u>	<u>Strengths (mg/tablet)</u>			
	<u>100 mg</u>	<u>50 mg</u>	<u>25 mg</u>	<u>12.5 mg</u>
Captopril, USP	100.0	50.0	25.0	12.5
Lactose, NF				
Micro. Cellulose, NF				
Starch NF				
Palmitic Acid,				
Colloidal				
Silicon Dioxide, NF				
Talc, USP				
<u>Total:</u>	<u>400 mg</u>	<u>200 mg</u>	<u>100 mg</u>	<u>50 mg</u>

Comments:

1. Results of the in vivo bioequivalence study conducted on the 100 mg tablets of the test and the reference products indicate that the differences in AUC_{0-4} , $AUC_{0-\infty}$ and C_{MAX} were less than 4% and insignificant. The 90% confidence intervals for $LnAUC_{0-T}$, $LnAUC_{0-\infty}$ and LnC_{MAX} of the test product remained within the 80% to 125% limit of the corresponding reference mean values. However, the firm has failed to submit the following information:
 - a) Potency of the test and reference tablets.
 - b) Condition for Dissolution Testing, such as, USP apparatus, speed, solvent, volume of solvent, assay methodology, specification of dissolution, etc.
 - c) The reference product, 100 mg Capoten^R tablets of lot #H3J73A was used in bio-study but the reference product used in dissolution testing was from different lot (#B3J73A). The product from same lot should be used in both bioequivalence study and dissolution testing.
2. The firm is required to provide information on the QC samples, such as, when these samples were prepared, how long these samples were stored and at what temperature they were stored, etc.
3. The firm should be requested to provide information on the extraction procedure of captopril from whole samples and the

4. The firm is requested to submit all statistical analyses (detailed ANOVA analysis) conducted on the test and reference samples (mean) collected at each sampling time.
5. The in vivo bioequivalence study conducted on the 100 mg tablets of the test and reference products is incomplete.
6. The in vitro dissolution testings conducted on 100 mg, 50 mg, 25 mg and 12.5 mg Captopril Tablets are incomplete.
7. The firm should be advised to submit the formal waiver request for in vivo bioequivalence studies on 50 mg, 25 mg, and 12.5 mg Captopril Tablets manufactured by Wockhardt Ltd.

1. The in vitro dissolution testing and the in vivo bioequivalence study conducted by Wockhardt Ltd. on its 100 mg Captopril Tablets, Lot # 94001-D, versus the listed reference product, Capoten[®] 100 mg Tablets manufactured by Squibb have been found incomplete by the Division of Bioequivalence for the reasons stated in Comments #1-6 above.
2. The in vitro dissolution testings conducted on 50 mg, 25 mg and 12.5 mg test tablets are incomplete due to the reasons cited in Comment #1.
3. The firm should be advised of the Comments and Recommendations, above.

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Date: ---/---/---

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Figure 1

Project No. 940306

Mean Whole Blood Unchanged Captopril Concentrations

(Semi-Log Plot)

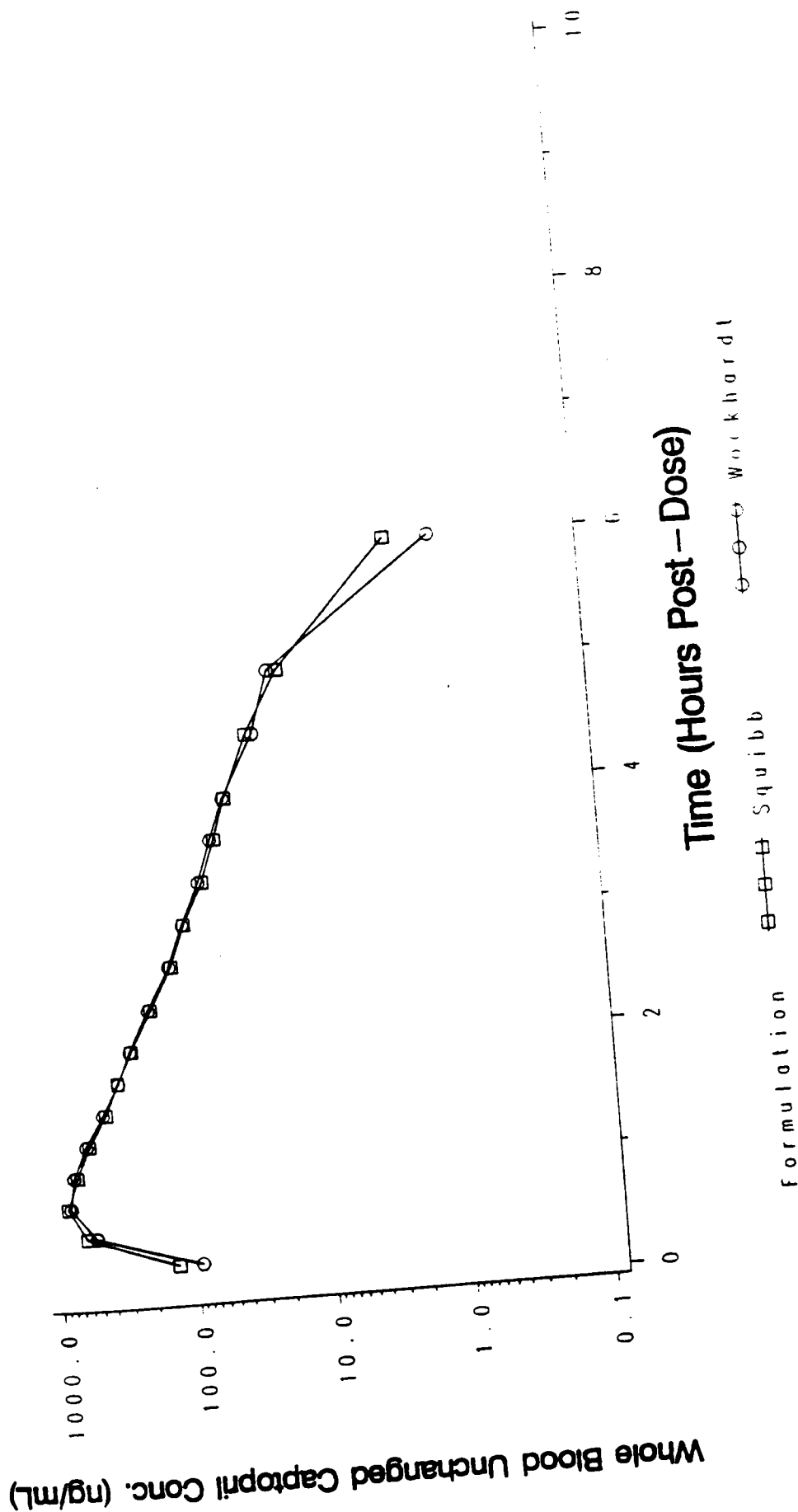


Figure 2
Project No. 940306
Mean Whole Blood Unchanged Captopril Concentrations
(Linear Plot)

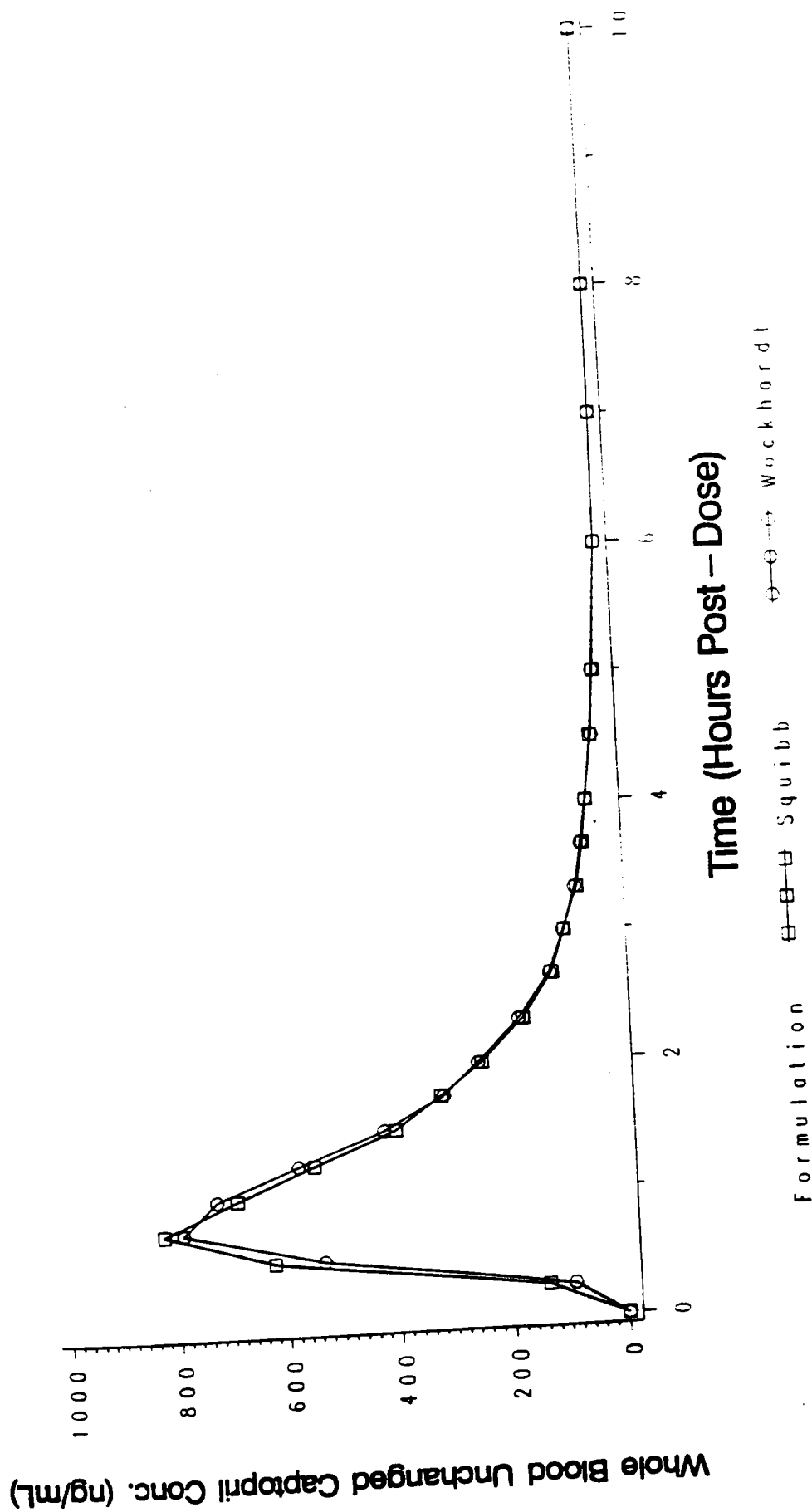


TABLE 1

MEDICAL EVENTS

Subject	Period	Dosing	Time/Date	Sign/Symptom		Time after dosing	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up	
				Dur-	at-								Time	Int-
				after dosing									Evolution	Intensify

8 1 09:14: 31/03/94 Dizziness (DIZZINESS/NER)

5.0h NS 16.5h E D PR E M 12.1h U M None
22.3h R N/A

23 1 09:44: 31/03/94 Flatulence (FLATUL/DIG)

6.7d NS 2.0h E O PR SP M 6.8d R N/A

Cause undetermined.

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d-Days	S-Serious	E-Expected	D-Drug	D-Definite	E-Elicited	M-Mild	I-Increased	N/A - Not Applicable
h-Hours	NS-Non-Serious	U-Unexpected	P-Procedure	PR-Probable	SP-Spontaneous	MO-Moderate	U-Unchanged	N/R - Not Recorded
m-Minutes			O-Other	PO-Possible	O-Observed	S-Severe	D-Decreased	
				U-Unlikely			R-Resolved	

A - Mochhardt 1 x 100 mg captopril tablet

B - Squibb (Capoten) 1 x 100 mg captopril tablet

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Subject	Period	Dosing	Time/Date	Sign/Symptom		Time after dosing	Seriousness	Likelihood	Causality	Probability	Report method	Intensity at Onset	Follow-Up	
				Time after dosing	Dur- ation								Time after dosing	Action / Comment

9 2 09:16: 07/04/94 Feels heart beating faster (TACHYCARDIA/CV)

2.0h NS 25.0m E D PR SP M
2.2h N/A N/A BP: 108/60 Pulse: 76
2.3h U M None
2.4h R N/A BP: 98/56 Pulse: 56

TIME UNITS	SERIOUSNESS	LIKELIHOOD	CAUSALITY	PROBABILITY	REPORT METHOD	INTENSITY	EVOLUTION	GENERAL
d-Days	S-Serious	E-Expected	D-Drug	D-Definite	E-Elicited	M-Mild	I-Increased	N/A - Not Applicable
h-Hours	NS-Non-Serious	U-Unexpected	P-Procedure	PR-Probable	SP-Spontaneous	MO-Moderate	U-Unchanged	N/R - Not Recorded
m-Minutes			O-Other	PO-Possible	O-Observed	S-Severe	D-Decreased	
				U-Unlikely			R-Resolved	

A - Mochhardt 1 x 100 mg captopril tablet

B - Squibb (Capoten) 1 x 100 mg captopril tablet

24-05-1994

Table 4
Project Number : 940306
Unchanged Captopril in Whole Blood
Ratio Analysis - AUC 0-t (ng·h/mL)
Mockhardt (A) vs Squibb (B)

14:53

Subject	(A)	(B)	(A/B)%
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
Arithmetic Mean	1124.4	1139.5	99.59
± SD	167.02	185.11	12.637
CV%	14.9	16.2	12.7
n	24	24	24

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24-05-1994

14:53

Table 5
Project Number :940306
Unchanged Captopril in Whole Blood
Ratio Analysis - AUCinf (ng·h/mL)
Hockhardt (A) vs Squibb (B)

Subject	(A)	(B)	(A/B)%
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
Arithmetic Mean	1159.0	1172.8	99.67
± SD	168.06	186.98	11.988
CV%	14.5	15.9	12.0
n	24	24	24

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24-05-1994

14:53

Table 6
Project Number :940306
Unchanged Captopril in Whole Blood
Ratio Analysis - Cmax (ng/mL)
Wockhardt (A) vs Squibb (B)

Subject	(A)	(B)	(A/B)X
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
Arithmetic Mean	840.49	870.18	101.56
± SD	151.782	206.820	30.836
CV%	18.1	23.8	30.4
n	24	24	24

PHAST RTAB 2.2-003

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